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(54) Title: COMBINATION THERAPY FOR DEPRESSION, PREVENTION OF SUICIDE, AND VARIOUS MEDICAL AND PSYCHIATRIC CONDITIONS

(57) Abstract: The present invention relates to a new method of treatment for persons meeting diagnoses for major depressive disorder, or other unipolar (non-bipolar, nonpsychotic and non-treatment resistant) depression. The method comprises administering a combination of two categories of drugs, antipsychotics or dopamine system stabilizers, in combination with a newer antidepressant such as a selective serotonin reuptake inhibitor, as initial treatment or as soon as possible. The method targets the prevention of suicide, and provides other benefits including preventing disease progression development of tolerance toward the antidepressants. Another aspect of the invention relates to using the method for alleviating cognitive distortion and related functional impairment or health risks, and/or using the method for smoking cessation or nicotine withdrawal.

WO 2004/010932 A2

COMBINATION THERAPY FOR DEPRESSION, PREVENTION OF  
SUICIDE, AND VARIOUS MEDICAL AND PSYCHIATRIC CONDITIONS

CROSS-REFERENCE TO RELATED APPLICATION

5           This application claims priority under 35 USC § 119(e) to Provisional Application Serial No. 60/319,436, filed July 30, 2002, entitled "New Approaches to the Treatment, Assessment and Research of Depression", explicitly incorporated herein by reference.

FIELD OF THE INVENTION

10           The present invention relates to a new method of treatment for persons diagnosed with unipolar depression, including major depressive disorder, dysthymic disorder, and/or dual depression. The method may also be used to treat depression NOS, substance/alcohol induced mood disorder (depression), postpartum depression, adjustment disorder with depressed mood, cognitive distortions, smoking  
15           cessation or nicotine withdrawal.

            The method comprises administering an antipsychotic drug, preferably an atypical antipsychotic or dopamine system stabilizer, in combination with a newer antidepressant such as a selective serotonin reuptake inhibitor, or other newer antidepressants.

BACKGROUND INFORMATION

20           The rate of depression has been rising over the years. It affects 17.6 million Americans every year, robbing people of a fulfilling life with a cost of about \$44 to \$52.9 billion annually. It carries the risk of suicide with 30,000 to 35,000 deaths a year, a rate that resembles the death rate from leukemia.

25           The first treatments for severe mental disturbances became available in the 1930's, when extracts from the plant rauwolfia serpentina were used for the amelioration of psychotic symptoms. Major advances in the treatment of psychosis, however, did not come until 1950 with the discovery of chlorpromazine. The first generation of antidepressants did not become available until the 1950's, and included  
30           monoamine oxidase inhibitors and tricyclic antidepressants. While chlorpromazine was used early on in the treatment of depression, as tricyclic antidepressants became available the use of antipsychotic medications declined, and they were never widely

used in the treatment of depression in the absence of psychotic symptoms. See also Raskin A. et al 1970, p.170: "There is a persistent belief that these drugs (antipsychotics) are not very effective in the treatment of depression". In general, the use of antipsychotic drugs was reserved for use in patients having psychotic symptoms. It was generally accepted that antipsychotic drugs used alone could not treat major depressive disorder. In fact, it was thought that antipsychotic drugs, including some of the atypical antipsychotics, may even have depressogenic properties. (Harrow, M. et al 1994, Galdi J. 1983, Tollefson, G.D. et al 1998, Maguire, G.A. 2002, Cookson I.B. et al.)

10 In contrast to antidepressants, antipsychotics alone (including the atypical antipsychotic risperidone) were ineffective in the chronic mild stress (CMS) model (animal simulation of depression) (Papp, M. et al 1996; Papp, M. et al 2000). In sum, many studies showed that antipsychotics do not have significant antidepressant activity and, if anything, may cause a depressogenic effect.

15 Due to the severe side effect profiles of the traditional antipsychotic drugs, the risks of taking these drugs, in the absence of their specific indications (such as psychosis, severe agitation or anxiety) were believed to be unwarranted by the medical community. (Price, L.H. et al. 2001. p. 207.)

20 Such risks included side effects such as tardive dyskinesia (TD), a potentially irreversible effect involving involuntary movement or other dyskinetic movements, or the rare but potentially fatal neuroleptic malignant syndrome (NMS). Many states (e.g. MN) require written consent forms from patients prior to starting an antipsychotic medication in inpatient psychiatric settings, and some outpatient clinics have also adapted that policy.

25 Early reports compared the antidepressant efficacy of two older/traditional groups of medications, the tricyclics (TCA) and traditional antipsychotics, or their use in combination, (Robertson, M., et al. 1982; Hollister, 1967). This review by Robertson (Robertson, M.M. et al. 1982) was based mostly on studies with mixed-anxiety depressive states, now more appropriately called as depression with anxiety as a comorbid disorder (Zimmerman, 2002). The combination use had been reserved for psychotic depression. A later review summarized the opinion, that "while a 'true' antidepressant effect has been demonstrated for the

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tricyclic antidepressants, similar effects appear doubtful for the antipsychotic drugs.” (Nelson, J.C., 1987).

The combination use of these medications to treat non-treatment resistant, and non-psychotic depression was never recommended. A book chapter reviewing this topic from year 2001 makes the point that “the risk/benefit ratio in refractory patients lacking such features [as near-psychotic rumination or marked psychomotor agitation] generally does not favor [antipsychotic augmentation]”. (Price, H. 2001,). The reports available up to date have reserved the combination use of antidepressant-antipsychotics only for psychotic depression, or for treatment-resistant depression.

More recently, with the development of new atypical antipsychotic medications, there have been reports of using an atypical antipsychotic in combination with an antidepressant, such as an SSRI (selective serotonin reuptake inhibitor), to treat a specific subgroup of depressed patients that do not respond to antidepressants alone, that is, patients who have treatment-resistant depression (TRD). See, for example, WO 99/61027, which describes the use of SSRI's and atypical antipsychotics for partially-responding or treatment-resistant depression. Shelton, C. R., et al: 2001; Ostroff, R.B. et al: 1999; Alpert, J.E., et al.: 2002; Parker, G., 2002; Pitchot, W., et al 2001; O'Connor, M. 1998; Kaplan, M. 2000. See also reviews on the combined use of atypical antipsychotics and SSRIs for treatment resistant depression (Thase 2002). Nierenberg (Nierenberg. A. A., 1992) had noted that the cause of treatment-resistant depression may be an unrecognized psychosis, that may explain – at least in part – of why the “treatment-resistant” depression group improved with the addition of an antipsychotic medication.

As used herein, the term “treatment-resistant” is used as that term is understood by one skilled in the art, and as used in the present invention, means a lack of therapeutic response after at least one trial of an antidepressant at an adequate dose for six weeks.

While the newer drugs referred to as atypical antipsychotics have improved side effect profiles as compared with traditional antipsychotics, especially as regards to NMS, TD and acute extrapyramidal symptoms (EPS), they too can produce undesirable side effects, including potentially serious adverse effects not

always present with some of the typical (older) antipsychotics. These adverse effects include agranulocytosis, (specifically with clozapine), neutropenia, seizure, weight gain, hyperglycemia, diabetes, diabetic ketoacidosis as a first sign of diabetes, hyperlipidemia/hypercholesterolemia, hyperprolactinemia (with potential consequent  
5 bone loss, depressive effect, and sexual dysfunction), orthostatic hypotension, tardive dyskinesia (TD) an involuntary movement, EPS, NMS, in EKG a prolongation of QTC interval with the potential of life threatening arrhythmia (ziprasidone), and other adverse effects (dry mouth, sedation, increase in appetite, asymptomatic elevations in liver enzymes, hypersalivation, tachycardia, hypotension, hypertension, constipation,  
10 and urinary incontinence). In addition, there are also some rare side effects associated with the atypical antipsychotics, such as priapism, rabbit syndrome, chorea, eosinophilia, Pisa syndrome, periodic leg movements and restless legs syndrome, and sudden death in patients receiving clozapine. There have also been reports of mania, and withdrawal syndromes.

15 Therefore, when combining antipsychotics with antidepressants it should be noted that some of their adverse effects may add up, or may present with new risks. These added or new risks may include the increase in weight; risk factor for diabetes, cardiac and other medical morbidity and mortality; hyponatremia, an electrolyte disturbance; TD; akathisia and extrapyramidal symptoms (EPS); and the  
20 potentially dangerous serotonin syndrome.

The atypical antipsychotics and dopamine system stabilizers are also expensive drugs. Thus, to date, the use of atypical antipsychotic medications has been restricted to their use in combination with antidepressants, for the treatment of the following subtypes of illness: schizoaffective disorder; psychotic depression; bipolar  
25 (manic-depressive) disorder; and treatment-resistant depression. In all of these categories, the use of antipsychotic medication may be expected due to its effects on contributory psychosis, or severe agitation.

There have been no reports recommending that the combination therapy can or should be used for a major depressive disorder, or for other depressions  
30 as an initial treatment, upon initial presentation to a health care provider (or as soon as possible), or for using the combination as a treatment of first choice, for reducing the risk of suicide.

Standard therapeutic methods of treating persons suffering from various types of depression, including major depressive disorder, who are at risk for suicide, and in particular those who are at high risk of suicide remain inadequate. There remains a need for an initial form of treatment to reduce the risk of suicide and other pathologies associated with depression, and in particular with major depressive disorder.

Effective methods of treating the symptoms associated with smoking cessation and nicotine withdrawal are similarly lacking. Unfortunately, smoking cessation rates at 1 year are very low, for the nicotine transdermal system (patch) it is 16.4%, for bupropion (Zyban) it is 23-30% (and with their combination is still only 28-35%). The smoking cessation rate is low even with the educational programs by the American Lung Association (19.0%-24.8%) or by the American Cancer Society (12.1-22.4%) (Migaly, P. smoking cessation book in progress). Therefore there is a need for improvement.

Different aspects of smoking cessation and treatment of nicotine withdrawal had been addressed before. U.S. Patent No. 5,780,051 addresses the issue of antidepressants (including bupropion) with some other criteria; U.S. Patent No. 6,582,737 addresses the use of bupropion with different criteria. U.S. Patent No. 5,780,051 addresses the issue of antipsychotics including olanzapine, with some other criteria, and U.S. Patent No. 6,159,963 also addresses the use of olanzapine in the treatment of nicotine dependence, and for withdrawal syndrome, again together with some other criteria.

None of the prior art has suggested the combination of low dose atypical antipsychotics or dopamine system stabilizers with newer antidepressants for treatment of smoking cessation and nicotine withdrawal, or the need to target cognitive distortions with this combination. However, the combination of these categories of medications are likely to potentiate each other and to provide an increased effectiveness.

#### SUMMARY OF THE INVENTION

The present invention addresses the above need and provides a method of treating persons having depression, major depressive disorder and, in particular, those at high risk of suicide. The method comprises administering an effective

amount of an antipsychotic medication or dopamine system stabilizer in combination with a newer antidepressant, to patients who have *not* been diagnosed as treatment-resistant, or bipolar disorder, and who do *not* have psychotic symptoms. Preferably the antipsychotic medication is an atypical antipsychotic. In one embodiment, the  
5 antidepressant is a selective serotonin reuptake inhibitor. Furthermore, this combination may specifically target the prevention of suicide.

The present invention provides the following benefits: preventing disease progression/modifying the course of depression, delaying/preventing relapse or recurrence of depression, preventing the development of delusional/psychotic  
10 depression, being protective/(and/or) remedying the development of tolerance toward the antidepressant, and a possibility for providing a neuroprotective effect. It may also provide a more effective treatment, increase the response rate to treatment, treat the residual symptoms of depression, prevent the antidepressant's paradoxical effect of sensitizing patients to depression and relapse, and prevent the worsening of  
15 depression caused by the antidepressants.

It is an object of the present invention, therefore, to provide a method of initial treatment of a patient suffering from major depressive disorder, by administering an antipsychotic medication or a dopamine system stabilizer, in combination with a newer antidepressant.

20 It is a further object of the present invention to provide a method of treatment for major depressive disorder, in a patient who meets the diagnostic criteria, (or the depression types covered in this invention,), but is not on an antidepressant yet, or has not been in treatment long enough or does not meet criteria otherwise for treatment-resistant depression, or psychotic depression. The method comprises  
25 administering the combination of antidepressant - atypical antipsychotic, or antidepressant-dopamine system stabilizer medications, started as soon as possible, as an initial treatment.

It is an additional object of the present invention to provide a method of treating a patient suffering from unipolar depression, including major depressive  
30 disorder, to reduce the risk of suicide.

In an additional aspect, the present invention provides a method of treating a patient where the patient may or may not have any depression, the method

comprising administering to said patient an effective amount of a newer antidepressant in combination with a low dose of an antipsychotic drug, atypical antipsychotic drug, or a dopamine system stabilizer; wherein treatment is given to decrease cognitive distortions, to alleviate related functional impairment or serious health hazards, and provide benefit in any and all of the corresponding disorders, to which cognitive distortions contribute.

In yet another additional aspect, the present invention provides a method of treating a patient where the patient may or may not have any depression, the method comprising administering to said patient an effective amount of a newer antidepressant in combination with a low dose of an antipsychotic drug, atypical antipsychotic drug, or a dopamine system stabilizer; wherein treatment is given for smoking cessation or nicotine withdrawal.

These and other objects of the invention will become more readily apparent from the following detailed description and appended claims.

#### DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS

The present invention provides a method for initial treatment of a patient suffering from major depressive disorder, or other unipolar depression, including but not limited to, dysthymic disorder, dual depression, depression NOS, substance/alcohol induced mood disorder (depression), postpartum depression, adjustment disorder with depressed mood. As used herein, the term "unipolar depression" will refer to any of these types of depression. The method can also be used for treatment of cognitive distortions, smoking cessation or nicotine withdrawal. The method comprises administering an effective amount of a newer antidepressant in combination with an antipsychotic drug, to a patient in need of such treatment. In a preferred embodiment, the antidepressant is an SSRI, and the antipsychotic drug is an atypical antipsychotic drug, or a dopamine system stabilizer. Most preferably, the combination comprises fluoxetine and risperidone. Specifically, the patient is not treatment resistant, as that term is understood in the art, and does not have psychotic symptoms, such as delusions or hallucinations.

Excluded from the depression types covered under the present invention are bipolar (manic-depressive) disorder, delusional or psychotic depression,



depression with psychotic features, depression occurring in psychotic disorders, and treatment-resistant depression.

In one embodiment the antidepressant can be any of the newer antidepressants, and the antipsychotic can be any of the atypical antipsychotics or  
5 dopamine system stabilizers.

In yet another embodiment, the antidepressant can be any of the newer antidepressants and the antipsychotic medication can be switched later to a dopamine system stabilizer. This can occur through tapering off or the sudden discontinuation of the antipsychotic with the start of the dopamine system stabilizer, or through a "cross  
10 taper" over a period of a time.

If an antipsychotic is used with a newer antidepressant, then it should be preferably given at a low dose and selected to also have a strong anxiolytic property. A low potency antipsychotic such as perphenazine (Trilafon) at a low dose is an option if the atypical antipsychotic or dopamine system stabilizer cannot be  
15 used. High potency antipsychotics have a particularly high risk for TD. Trifluoperazine (Stelazine) (at a low dose) may be considered to be a substitute if used for a short time. Haloperidol (Haldol) is not recommended as a preferred application as it is likely to be depressogenic.

Other antipsychotics (with some unusual characteristics) like  
20 amipsulpride, sulpiride or flupenthixol, that do not meet the atypical criteria of higher serotonin to dopamine affinity, may also be used in combination with antidepressants as an *initial* treatment.

It is thought that initial treatment of an individual suffering from major depressive disorder with the combination therapy of the present invention can  
25 dramatically reduce the risk of suicide, and provide many other advantages.

In particular, it is thought that the present combination therapy is especially beneficial in persons diagnosed with major depressive disorder and in persons with unipolar depression, who have thoughts of suicide, or are at risk of suicide. Those patients who present in acute settings, like in ER, would be particularly  
30 good candidates for the combination therapy. However, all depressed patients are at risk of suicide.

As used herein, "effective amount" means the amount of drug necessary to provide a therapeutic benefit, such as substantial improvement in mood and relief from symptoms of depression, the amount necessary to provide prevention of suicide, or to achieve the other benefits of the combination listed above.

5 Determination of the appropriate dosage is well within the ability of one skilled in the art; antidepressants and antipsychotics have been prescribed for years. When used in the combination of the present invention, dosage of the antidepressant will be similar to the dosage amount needed when prescribed alone, while the amount of antipsychotic drug needed will be somewhat less than the amount used when that  
10 class of drug is prescribed alone for a patient experiencing psychotic symptoms. In the method of the present invention, the dosage of the antipsychotic drug should be around approximately one-third (1/3) to the average dose of the amount normally prescribed. However, a lower than average dose is preferred for most cases. At times minimal dose can be expected to be sufficient, like for quetiapine 25-50mg, (if needed  
15 raised up to 300-400 mg q.d.), for risperidone 0.5-1mg (if needed raised to 2-4 mg q.d.), for olanzapine 2.5 mg-5mg, (and at times used at 10 mg q.d.), or for ziprasidone 10-20mg (at times at 40mg), and most likely, for aripiprazole 2.5-10 mg q.d. or less; (if needed given at 15mg q.d.) as an example.

It should also be understood that these doses are not fixed, and a lower  
20 dose may be effective for some, but not for others. In the case of the atypical antipsychotics and dopamine system stabilizers, a higher dose (similar to the doses given for psychosis) may be effective in the prevention of suicide. The exceptions from this are the doses when EPS and other side effects occur. However, it is best to expose the patient to the least amount of effective medication. In addition lower doses  
25 may have other benefits as well.

Suitable dosage forms include capsules, tablets, and the like, preferably for oral administration, although any dosage form, for any route of administration is contemplated. The combination therapy can be administered as separate entities, e.g. two tablets or other forms, each containing one drug, or may be administered as a  
30 single dosage form containing both drugs (i.e. within the same delivery system), or concomitant use, (e.g. within 5 minutes).

In case of oral administration of the different medication components, the single dose can be, but is not limited to a (single) capsule, tablet (including "sprinkle", fast dissolving, "melt away"), or oral solution, and it may also contain inactive component(s) that is necessary to form the single delivery system.

5           The medications (with different medication components) can also be administered by other routes, not limited to oral intake. For example, administration can be transdermal (patch), buccal, sublingual, topical, nasal, parenteral (subcutaneous, intramuscular, intravenous, intradermal), rectal, vaginal, administration. Various combinations of controlled release/rapid release are also  
10 contemplated.

As used herein, the term "partial response" is used as that term is understood in art, and refers to 25-49% improvement from baseline on recognized depression rating scales (Hirschfeld, R.M.A. et al 2002). Response to treatment refers to an improvement of at least 50% in depression scales, and non-response refers to  
15 improvement of less than 25% (Hirschfeld, R.M.A. et al 2002).

It is possible to have a response to an antidepressant treatment (i.e. better than a partial response or non-response), but still have residual symptoms, and not a full recovery. Therefore the combination may also be effective to treat residual symptoms of depression (which is a separate entity and not equal to partial response),  
20 to achieve full remission as a goal. In this case the risk/benefit analysis of giving a medication combination is also different from TRD.

Major depressive disorder may also be accompanied by many relapses. The combination treatment of the present invention may delay or prevent relapse, be prophylactic for the recurrence of depression; prevent disease progression and modify  
25 the course of depression. The combination treatment may also prevent the progression of the disease and modify the course of depression by preventing the development of delusional/psychotic depression; or by being protective against, and/or remedying the development of tolerance toward the antidepressant, when the antidepressant has lost its effectiveness.

30           In addition, depression may emerge during treatment with antidepressants in non-depressed patients (Fux, M. et al 1993, Fava, G.A. 2003,), and antidepressants may have a paradoxical effect and may be sensitizing patients to

depression or relapse. (DiMascio, A. et al 1968, Fava, G.A. 2003). The combination treatment may also be protective for this phenomenon. The combination treatment may help avoiding the worsening of depression caused by the antidepressants.

As used herein, the term "major depressive disorder" (MDD) is used as that term is understood in art, and refers to a diagnosis that is guided by diagnostic criteria listed in DSM-IV or ICD-10, or in similar nomenclatures. (DSM-IV-TR., 2000, Kaplan, H.I. et al. 1998.) There are also some exclusion criteria for both the major depressive episode, and MDD. Major depressive episode can be a building block to diagnose MDD and other mood disorders (e.g. bipolar disorder), and it is not specific to MDD. However, DSM IV requires for the diagnosis of MDD the presence of a major depressive episode. This in turn consists of at least five of the nine symptoms present during the same 2-week period, of which depressed mood or loss of interest or pleasure has to be one of the symptoms. Changes in weight/appetite, sleep, energy, psychomotor retardation or agitation, guilt, decreased concentration, suicidality are the other symptoms. One does not need to have all of the symptoms present for the diagnosis, and MDD or major depressive episode is therefore not equal to the individual symptoms, as some may be absent. Suicidal thought is one of the depressive signs tested and need not to be present for the diagnosis of MDD.

The definition of other diagnostic terms referenced here are also used as they are understood in the art, and refer to diagnoses that are guided by diagnostic criteria listed in DSM-IV or ICD-10, or in similar nomenclatures. (DSM-IV-TR., 2000, Kaplan, H.I. et al. 1998.)

It should also be noted that depression is not the only psychiatric disorder leading to suicide. Other disorders like bipolar disorder, psychotic disorders (like schizophrenia), anxiety disorders (including panic disorders, OCD, PTSD), alcohol and drug addictions, and personality disorders may also lead to suicide.

As used herein, the term "patient" means a person who has sought or is in need of medical or appropriate treatment and is under the care or would need to be under the care of a physician(s) or health care provider(s), or is in need of treatment.

As used herein, the term "newer antidepressants" is used as that term is understood in the art, and generally refers to antidepressants excluding traditional tricyclic or tetracyclic antidepressants and excluding MAO (permanent inhibitor).

Specifically, the newer group of antidepressants includes, but is not limited to, serotonin reuptake inhibitors, selective norepinephrine reuptake inhibitors (SNRI), combined action SSRI/SNRIs, SARIs (serotonin-2 antagonist/reuptake inhibitors), alpha-2 antagonists plus serotonin-2 and serotonin-3 antagonists, serotonin/norepinephrine/dopamine reuptake inhibitors, norepinephrine and dopamine reuptake inhibitors or other antidepressants. These include but are not limited to fluoxetine (Prozac), norfluoxetine, paroxetine (Paxil), sertraline (Zoloft), fluvoxamine (Luvox), citalopram (Celexa), escitalopram (Lexapro), bupropion (Wellbutrin), nefazodone (Serzone), mirtazapine (Remeron), venlafaxine (Effexor), duloxetine, clomipramine, milnacipran, S33005, reboxetine, nisoxetine, zimelidine, litoxetine, indalpine, gepirone, femoxetine, alaproclate, and racemic forms or derivatives thereof, and pharmaceutically acceptable salt thereof.

Antidepressants also included are:

Serotonergic compounds like 5-HT-1alpha- antagonist (for example NAD-299) and 5-HT-1beta antagonist (for example AR-A2); 5-HT1A receptor agonists and antagonists; 5-HT2 receptor antagonists, Vivalan (viloxazine hydrochloride); AZD4282 (oral glycine); Dehydroepiandrosterone (DHEA) with NMDA potentiating effect, or other NMDA receptor antagonists. Other examples of the NMDA receptor antagonists include, but are not limited to, dextromethorphan, dextrorphan, ketamine, amantadine, memantine. Also included are AMPA receptor potentiators, e.g. LY392098; substance P antagonists / neurokinin-1 (NK-1) receptor antagonists, for example, Merk's MK-869; Pfizer's CP122,721; nonpeptide Substance P antagonist; Merk's compound A; aprepitant (MK-0869); or NKP608, L-760735, L-733,060, GR205171; neurokinin 2 antagonists; neurokinin 3 antagonists; corticotropin-releasing factor receptor antagonists like R121919, antiglucocorticoid medications, glucocorticoid receptor antagonists, agents blocking cortisol, e.g., ketoconazole, metyrapone, aminoglutethimide, mifepristone [Mifeprex] (RU486); nitric oxide synthase inhibitors; inhibitors of phosphodiesterase; enkephalinase inhibitors; GABA-A receptor agonists; agents with neuroprotective effects such as NXY-059, a free radical trapping agent; atypical MAOI's like Selegiline (or transdermal Selegiline); selective MAOI inhibitors like moclobemide, brofaromide, befloxatine, cimoxatone, toloxatone, amiflamine, harmaline derivatives, clorgyline;

hormones: in males testosterone; in females estrogen/estradiol; omega-3 fatty acids; other products with antidepressant effects such as folinic acid, leucovorin, tramadol (Ultram); or substances that may enhance 5-HT synthesis and/or antidepressant effects including, but not limited to tryptophan.

5                   As understood herein, the term "atypical antipsychotics" refers to drugs having a higher 5-HT<sub>2</sub> affinity and a relative lower D<sub>2</sub> affinity as compared with other typical antipsychotic drugs. They also show low EPS compared to typical (conventional) antipsychotics. Atypical antipsychotics include, but are not limited to, clozapine, quetiapine, risperidone, ziprasidone and olanzapine, and Org 5222,  
10 melperone, amperozide, iloperidone, SM-9018, JL-13.

                  The various atypical antipsychotics have a diverse receptor binding profile and they are not only differ from each other but also from the dopamine system stabilizer aripiprazole. (Kane, J.M. 1997, Lawler, C.P. et al 1999, Yokoi, F. et al 2002, Bymaster, F.P. et al 1996, Seeger, T.F. et al 1995, Szewczak, M. et al 1995,  
15 Arnt, J. et al 1998.)

                  As used herein, the term "dopamine system stabilizer" is used as that term is understood by one skilled in the art. Dopamine system stabilizers preserve or enhance dopaminergic neurotransmission where it is low, and reduce it where it is too high. This is accomplished through attaining a balance between presynaptic and  
20 postsynaptic D<sub>2</sub> receptor stimulation. Dopamine system stabilizers are antipsychotics, but the prototype dopamine system stabilizer, aripiprazole, does not meet the definition of "atypicality" as it does not have a higher 5-HT<sub>2</sub> affinity and a relative lower D<sub>2</sub> affinity. (See references above on receptor bindings).

                  Dopamine system stabilizers include, but are not limited to,  
25 aripiprazole, preclamol, tolipexole, terguride, roxindole and pharmaceutically acceptable salts thereof. Currently, only aripiprazole is approved for clinical use, and it is the prototype for dopamine system stabilizers.

                  It should be noted that if an antipsychotic shows a therapeutic effect on depressive or negative symptoms in schizophrenia, this does not mean that it would  
30 have an antidepressant effect in non-psychotics. Depression in psychosis (including psychotic depression), and depression in bipolar disorder (where psychosis is often predominant) are different categories from MDD or depression without psychosis.

These different diagnostic categories cannot be combined together in an analysis to study the antidepressant effect of any medication. (Ohaeri, J.U. 2000.)

Comparison of typical and atypical antipsychotics in psychotic patients (even at a similar dose) in their relative difference on negative symptoms or mood cannot be sufficient to assume an antidepressant property, and results cannot be extrapolate to patients where psychosis is not present.

The ability of the combination treatment to reduce the risk of suicide may be independent of (or at least not limited to) any action of the antipsychotic medications on mood. The combination of an antidepressant with an antipsychotic, preferably an atypical antipsychotic, is likely to be superior to an augmentation strategy with two antidepressants or to starting treatment with a single high dose antidepressant.

There are other strategies that target a faster onset of antidepressant action, (Montgomery S.A. 1997, Blier, P. et al 1997, Garattini, S. 1997,) and if these were equally effective on reducing the risk of suicide, they may be preferable due to their potentially less severe side effects. Stimulants are known to have fast onset antidepressant action, and are also used in combination for TRD (Ayd, F. et al 1987). Antidepressants with noradrenergic-serotonergic synergism, (either as a single antidepressant possessing these qualities, or as two antidepressants combined) have shown more rapid onset than SSRIs. (Glenberg, A.J. 2000, Quitkin, F. M. et al 2001, Nelson, J.C. et al 1991). Augmentation strategies used for treatment resistant depression could also be considered for initial treatment. However, the rapid onset antidepressant action is unlikely to give the same protection than the antidepressant-antipsychotic combination, and the risk of suicide is still present with the more rapid onset antidepressant strategies. Therefore the antidepressant-antipsychotic combination has a unique role in the prevention of suicide. No other combinations have been used for initial therapy; they are used in treatment resistant depression only.

If typical (or conventional) antipsychotics are used as adjunct to antidepressants a low dose should be given. The doses of the typical antipsychotics are also often given in "chlorpromazine equivalent" doses. (See e.g. conversion charts at DeBattista, C. et al 2003, p91; Jenkins S.C. et al 1990, p134). A low dose of an

antipsychotic would mean a chlorpromazine equivalent" dose of 25-50mg, or up to 100-150mg q d.

5 The antidepressant-(low dose) antipsychotic (in particular the atypical antipsychotic or dopamine system stabilizer) combination may also be used for the treatment of "cognitive distortion(s)", when the cognitive distortion(s) lead to functional impairment, or serious health hazard. The consequences may include of clinically significant distress, or impairment in important social, occupational, or other important areas of functioning, or deterioration of health.

10 The term "cognitive distortion" is used as it is understood in the art (Burns, D. 1980, Beck A, et al 1979, Beck, J. S, 1995, [p119.]), and may include overgeneralization, all or nothing (always-never) thinking, discounting positives or negatives, blaming and "labeling", assumptions and predictions, and emotional reasoning, all of which lead to "jumping to conclusions", without analysis of the facts.

15 Cognitive distortions may contribute to or worsen a number of illnesses like addictions, smoking, pathological gambling, impulse control disorders, anger, with consequent relationship (marital, work etc) conflicts, major depression, anxiety disorders (e.g., generalized anxiety disorder, panic disorder, OCD, PTSD), personality disorders, obesity, eating disorders (e.g. anorexia nervosa, bulimia nervosa), or possibly even some childhood disorders like oppositional defiant  
20 disorder, and conduct disorder.

If the method of the present invention is used for the treatment of cognitive distortions or smoking cessation/nicotine withdrawal, the criteria of the diagnosis of unipolar depression may not need to be present.

25 If the method is used for obesity/weight gain, or for smoking cessation (where there is also a risk of gaining weight) then an atypical antipsychotic like quetiapine or aripiprazole that is the least likely to increase weight should be chosen (olanzapine would be less preferable or even contraindicated). Similarly antidepressants with side effects of significant weight gain should be avoided.

#### EXAMPLES

30 The following examples are intended to illustrate the invention and should not be construed as limiting the invention in any way.



In the first hypothetical case a middle age male patient comes to the Family doctor with vague somatic complaints. Upon examination no physical problems are found, but in response to the doctor's screening questions about mood and depression the diagnosis of MDD is made. No psychosis or delusions are present.

5 There is no history of elevated mood or substance abuse. The patient does not meet criteria for treatment resistant depression, as he is not on any antidepressant. However, two years ago he had been on an antidepressant (fluoxetine 20 mg q.d.) for a year, while he was living in another state. He denies suicidal ideation or plans to the doctor. Family history is positive for depression, and one aunt had committed suicide.

10 Treatment alternatives are discussed with the patient and fluoxetine (20mg q d) and risperidone (1 mg q d) combination is chosen. The patient is also referred to cognitive therapy. The initial assessment of the therapist reveals that the patient uses significant amount of cognitive distortions (e.g. "all or nothing" [never/always] thinking, self-blaming, "labeling" self and others, predictions). In continuing with the medication

15 combination and therapy the patient makes a progress; his depression lifts and his cognitive distortions diminish in frequency and severity. The patient later reveals in therapy that he was feeling pretty hopeless and angry at his work situation and felt that "nothing else would help his situation than leaving this world". These symptoms (his suicidal thoughts) and his desperate feelings improved within a few days of the

20 medication combination "even before his depression went away".

In the second hypothetical example the patient is presenting herself to the emergency room (ER) after an argument with her family. MDD is diagnosed (without psychosis or delusions). Her 12 year old son is "oppositional, defiant", her teacher husband is jobless for 6 months but does not go to any job interviews. They

25 rarely talk to each other except the arguments. She feels she tried everything to improve her situation but now she wants to kill herself as a way out. She had been put on paroxetine (Paxil) 20mg q d two weeks ago by her Family doctor without much improvement (yet). Risk/benefits/alternatives are discussed in the ER with the patient, but she is reluctant to take any antipsychotics saying that "she is not crazy or

30 schizophrenic". Upon further education (and strong recommendation by the ER doctor) she is willing to try 50 mg of quetiapine (Seroquel) and actually takes the medication in the ER. It is than prescribed as 50 mg q HS. (There is no agitation

present.) She is admitted to the psychiatric department on a voluntary basis. In 24 hours her suicidality vanishes. She admits that she had contemplated suicide for several weeks now, and this was not related to yesterday's family argument. However she is complaining of lightheadedness and continues to express reluctance to take an antipsychotic. After discussion of alternatives and in the light of her improvement (that she is acknowledging), she is willing to switch from quetiapine to a dopamine system stabilizer (aripiprazole 5mg q HS), and does continue to do well on this. (She understands that this too is an antipsychotic, but the concept of dopamine system stabilizer is more acceptable to her). She also continues to take her paroxetine.

10 In both of the above patients the antipsychotic is discontinued in two months. Although some patients may show a relapse with the discontinuation of the atypical antipsychotic; the patients in both of these hypothetical cases continue to do well just on the antidepressant at the 10 months follow up. In the first patient the depressive symptoms return and the increase of fluoxetine is providing only temporary relief. At the 12 months follow up he is feeling very depressed again on 15 50mg of fluoxetine. Pharmaceutical tolerance to fluoxetine is assumed, and risperidone is restarted at 1mg q d with dramatic improvement within one week. Two months later this male patient notices galactorrhoea (milking of the breast) that is found due to the prolactin elevation from risperidone. Risperidone is discontinued, but 20 within a week his depressive symptoms return. He is then started on 50mg of quetiapine a day, and does well. Although the patient has a strong family history of recurrent major depression (despite of continuous SSRI intake in these relatives), he continues to do well on fluoxetine-quetiapine combination, and his depressive relapses are avoided at the 5 year follow up.

25 There may be many variations from the situations shown in these hypothetical examples. As in all treatment, the final decision is always up to the patient and the treating clinician. The continuation of antidepressant-antipsychotic combination beyond the acute phase may also need to be considered especially for the benefits of preventing disease progression (modifying the course of depression), preventing recurrence, preventing delusional/psychotic depression, providing a 30 neuroprotective effect, treat the residual symptoms of depression, preventing the development of tolerance toward the antidepressant (loss of its effectiveness), or

preventing the antidepressants paradoxical effect of sensitizing the patients to depression, worsening of depression or relapse.

Whereas particular embodiments of this invention have been described above for purposes of illustration, it will be evident to those skilled in the art that

5 numerous variations of the details of the present invention may be made without departing from the invention as defined in the appending claims. This may include the addition of other medications.

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What is Claimed Is:

1. A method for treatment of a patient suffering from major depressive disorder, the method comprising administering to said patient an effective amount of an antidepressant in combination with an antipsychotic drug, said major depressive disorder categorized as non-treatment resistant and non-psychotic.
2. A method for treatment of a patient suffering from unipolar depression, the method comprising administering to said patient an effective amount of an antidepressant in combination with an antipsychotic drug, said unipolar depression categorized as non-treatment resistant and non-psychotic.
3. A method for treatment of a patient having cognitive distortions with functional impairment or health hazards or of a patient undergoing smoking cessation or nicotine withdrawal, the method comprising administering to said patient an effective amount of an antidepressant in combination with an antipsychotic drug.
4. The method of Claims 1, 2, or 3, wherein said antipsychotic drug is an atypical antipsychotic.
5. The method of Claim 4 wherein said atypical antipsychotic drug is selected from the group consisting of quetiapine, risperidone, ziprasidone, and pharmaceutically acceptable salts thereof.
6. The method of Claim 4 wherein said atypical antipsychotic drug is selected from the group consisting of olanzapine, iloperidone, Org 5222, melperone, amperozide, SM-9018, JL-13, and pharmaceutically acceptable salts thereof.
7. The method of Claims 1, 2, or 3, wherein said antipsychotic drug is a dopamine system stabilizer.
8. The method of Claim 7, wherein said dopamine system stabilizer is aripiprazole, or pharmaceutically acceptable salts thereof.
9. The method of Claims 1, 2, or 3, wherein said antipsychotic drug is an antipsychotic administered at a low dose.
10. The method of Claim 9, wherein said antipsychotic drug is selected from the group consisting of perphenazine, trifluoperazine, zotepine, flupenthixol, amisulpride, and sulpiride.



11. The method of Claims 1, 2, or 3, wherein said antidepressant is selected from the group consisting of serotonin reuptake inhibitors, a selective norepinephrine reuptake inhibitors, combined action SSRI/SNRI, serotonin-2 antagonist/reuptake inhibitors, an antidepressant with alpha-2 antagonism plus serotonin-2 and serotonin-3 antagonism, an antidepressant with serotonin/norepinephrine/dopamine reuptake inhibition and an antidepressant with norepinephrine and dopamine reuptake inhibition.

12. The method of Claims 1, 2, or 3, wherein said antidepressant is selected from the group consisting of 5-HT-1alpha antagonist, 5-HT-1beta antagonist, 5-HT1A receptor agonists, 5-HT1A receptor agonists and antagonists, 5-HT2 receptor antagonists, viloxazine hydrochloride, dehydroepiandrosterone, NMDA receptor antagonists, AMPA receptor potentiators, substance P antagonists/ neurokinin-1 receptor antagonists, nonpeptide Substance P antagonist, neurokinin 2 antagonists, neurokinin 3 antagonists, corticotropin-releasing factor receptor antagonists, antiglucocorticoid medications, glucocorticoid receptor antagonists, cortisol blocking agents, nitric oxide synthetase inhibitors, inhibitors of phosphodiesterase, enkephalinase inhibitors, GABA-A receptor agonists, free radical trapping agents, atypical MAOI's, selective MAOI inhibitors, hormones, folic acid, leucovorin, tramadol, and tryptophan.

13. The method of Claims 1, 2, or 3, wherein said antidepressant is a selective serotonin reuptake inhibitor.

14. The method of Claims 11 or 13, wherein the antidepressant is selected from the group consisting of fluoxetine, norfluoxetine, paroxetine, sertraline, fluvoxamine, citalopram, escitalopram, bupropion, nefazodone, mirtazapine, venlafaxine, duloxetine, milnacipran, reboxetine, zimelidine, indalpine, gepirone, femoxetine, alaproclate and pharmaceutically acceptable salts thereof.

15. The method of Claims 11 or 13, wherein the antidepressant is clomipramine.

16. The method of Claims 1, 2, or 3, wherein said antidepressant is fluoxetine and said antipsychotic is risperidone.

17. The method of Claims 1, 2, or 3, wherein said antidepressant is fluoxetine and said antipsychotic is quetiapine.

18. The method of Claims 1, 2, or 3, wherein said antidepressant is fluoxetine and said antipsychotic is olanzapine.

19. The method of Claims 1, 2, or 3, wherein said antidepressant is fluoxetine and said antipsychotic is aripiprazole.

20. The method of Claims 1, 2, or 3, wherein said antidepressant is paroxetine and said antipsychotic is risperidone.

21. The method of Claims 1, 2, or 3, wherein said antidepressant is paroxetine and said antipsychotic is quetiapine.

22. The method of Claims 1, 2, or 3, wherein said antidepressant is paroxetine and said antipsychotic is olanzapine.

23. The method of Claims 1, 2, or 3, wherein said antidepressant is paroxetine and said antipsychotic is aripiprazole.

24. The method of Claims 1, 2, or 3, wherein said antidepressant is sertraline and said antipsychotic is risperidone.

25. The method of Claims 1, 2, or 3, wherein said antidepressant is sertraline and said antipsychotic is quetiapine.

26. The method of Claims 1, 2, or 3, wherein said antidepressant is sertraline and said antipsychotic is olanzapine.

27. The method of Claims 1, 2, or 3, wherein said antidepressant is sertraline and said antipsychotic is aripiprazole.

28. The method of Claims 1, 2, or 3, wherein said antidepressant is fluvoxamine and said antipsychotic is risperidone.

29. The method of Claims 1, 2, or 3, wherein said antidepressant is fluvoxamine and said antipsychotic is quetiapine.

30. The method of Claims 1, 2, or 3, wherein said antidepressant is fluvoxamine and said antipsychotic is olanzapine.

31. The method of Claims 1, 2, or 3, wherein said antidepressant is fluvoxamine and said antipsychotic is aripiprazole.

32. The method of Claims 1, 2, or 3, wherein said antidepressant is fluoxetine and said antipsychotic is ziprasidone.

33. The method of Claims 1, 2, or 3, wherein said antidepressant is paroxetine and said antipsychotic is ziprasidone.

34. The method of Claims 1, 2, or 3, wherein said antidepressant is sertraline and said antipsychotic is ziprasidone.

35. The method of Claims 1, 2, or 3, wherein said antidepressant is fluvoxamine and said antipsychotic is ziprasidone.

36. The method of Claims 1, 2, or 3, wherein the antipsychotic is selected from the group consisting of risperidone, quetiapine, olanzapine, ziprasidone and aripiprazole, and the effective amount is from 0.5mg to 4mg for risperidone, from 25mg to 400mg for quetiapine, from 2.5mg to 10mg for olanzapine, from 10mg to 40 mg for ziprasidone, and 2.5mg to 15 mg for aripiprazole.

37. The method of Claims 1, 2, or 3, wherein an effective amount of the antidepressant is its recommended therapeutic dose, or its effective starting dose.

38. The method of Claims 1, 2, or 3, wherein the administration is oral.

39. The method of Claims 1 or 2, wherein treatment is given as initial treatment or as soon as possible, or upon presentation to a physician or a health care provider.

40. The method of Claims 1 or 2, wherein treatment is given as initial treatment or as soon as possible, or upon presentation to a physician or a health care provider, and the said patient is at risk for suicide.

41. The method of Claims 1 or 2, wherein treatment is given for preventing suicide.

42. The method of Claims 1 or 2, wherein treatment is given for preventing disease progression, modifying the course of depression, delaying/preventing relapse, preventing the recurrence of depression, protecting against or remedying the development of tolerance toward the antidepressant, to provide a neuroprotective effect, to avoid a paradoxical effect of antidepressant to sensitize patients to depression, to avoid or treat worsening of depression from the antidepressant, to treat residual symptoms of depression, or for preventing the development of delusional/psychotic depression.

43. The method of Claims 1 or 2, wherein treatment is given as initial treatment or as soon as possible, or upon presentation to a physician or a health care provider for preventing suicide.

44. The method of Claims 4, 5, 6, 7, 8, 11 or 14, wherein treatment is given as initial treatment or as soon as possible, or upon presentation to a physician or a health care provider for preventing suicide.

45. The method of Claims 16 to 35, wherein treatment is given as initial treatment or as soon as possible, or upon presentation to a physician or a health care provider for preventing suicide.

46. The method of Claims 4, 5, 6, 7, 8 or 12, wherein treatment is given as initial treatment or as soon as possible, or upon presentation to a physician or a health care provider for preventing suicide.

47. The method of Claims 10, 11 or 14, wherein treatment is given as initial treatment or as soon as possible, or upon presentation to a physician or a health care provider for preventing suicide.

48. The method of Claims 16 to 35, wherein treatment is given for preventing disease progression, modifying the course of depression, delaying/preventing relapse, preventing the recurrence of depression, protecting against or remedying the development of tolerance toward the antidepressant, to provide a neuroprotective effect, to avoid a paradoxical effect of antidepressant to sensitize patients to depression, to avoid or treat worsening of depression from the antidepressant, to treat residual symptoms of depression, or for preventing the development of delusional/psychotic depression.

49. The method of Claim 3, wherein treatment is given for cognitive distortion(s), when the cognitive distortion(s) lead to functional impairment, or serious health hazard.

50. The method of Claim 3, wherein treatment is given for smoking cessation or nicotine withdrawal.